REMARKS

Claims 1 to 60 and 71 are all the claims pending in the application.

Claims 1-21 and 71 have been rejected under 35 U.S.C. § 103(a) as obvious over the Muller et al article in view of U.S. Patent 6,255,522 to Matsuo et al.

Applicants submit that Muller et al and Matsuo et al do not disclose or render obvious the subject matter of the above claims and, accordingly, request withdrawal of this rejection.

The present invention as set forth in claim 1 is directed to a process for producing an optically active α-substituted aminoketone represented by formula (4) or an optically active α-substituted aminoketone salt represented by formula (5), which has two asymmetric carbon atoms, the process comprising the steps of reacting an α-substituted ketone represented by formula (1) with an optically active amine represented by formula (2) to yield a mixture of diastereomers of an optically active α-substituted aminoketone represented by formula (3) and isolating one diastereomer from the mixture after optionally yielding salts of the diastereomers with an acid.

By employing an optically active amine as set forth in claim 1, since the obtained aminoketone forms diastereomers, one diastereomer can be easily separated from the other. Therefore, an optically pure compound can be obtained.

As set forth in dependent claim 9, the acid can be methanesulfonic acid.

The present invention as set forth in independent claim 71 is directed to a process for producing an optically active α-substituted aminoketone represented by formula (4) or an optically active α-substituted aminoketone of formula (5) by isolating one diastereomer from the

mixture of diastereomers of an optically active α-substituted aminoketone represented by formula (3) after optionally yielding salts of the diastereomers with an acid.

Applicants submit that Muller et al do not disclose a process for producing an optically active α-substituted aminoketone of formula (4) or an optically active α-substituted aminoketone salt of formula (5), and do not disclose or suggest the use of an optically active amine represented by formula (2) of the present claims.

In particular, Muller et al disclose a process for the reduction of a "racemic" α-phenylalkylamino propiophenone to produce a 2-phenyl alkylamino-l-phenylpropanol. See the title of Muller et al which specifically refers to the reduction of "racemic" α-phenylalkylamino propiophenone.

This process is illustrated broadly by equation (1) at page 450 of Muller et al where the α-phenylalkylamino propiophenone, which is a ketone, is designated with the reference numeral "1" (hereafter referred to as "compound 1"), and the 2-phenylalkylamino-l-phenylpropanol, which is an alcohol, is designated with the reference numeral "2" (hereafter "compound 2").

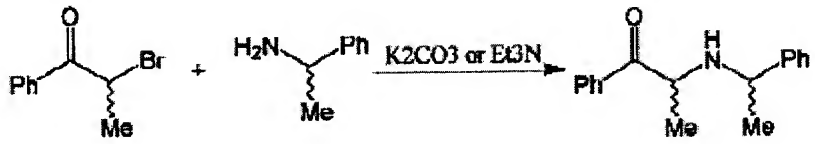
In the table at page 450, Muller et al disclose a number of different ketone compounds 1, among which is a compound 1b that satisfies the structure of formula (3) of the present claims, but which is not optically active. Muller et al also disclose compound 1b in the Table at page 452.

Muller et al, at page 451, lines 11 to 22, set forth a section that describes a process for producing ketone compounds 1, which Muller et al refer to as "AP-Derivatives," and at page 451, line 23+, sets forth a section that describes a process for producing the alcohol compounds 2.

Applicants now describe these sections of Muller et al which mainly include the following two reactions:

(1) Synthesis of α-phenylalkylamino propiophenone derivatives (AP-Derivatives)

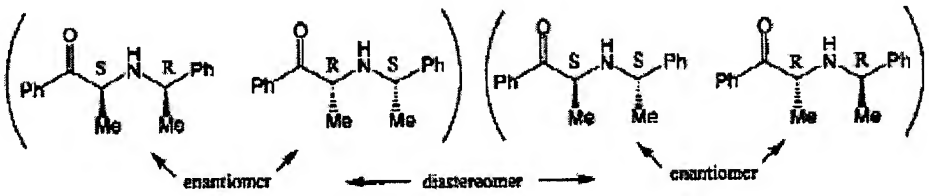
Muller et al state, at page 451, lines 11 to 22, that racemic α-bromopropiophenone is reacted with an amine compound (e.g. 1-phenylethylamine) in the presence of K_2CO_3 or triethylamine. Applicants illustrate this reaction as follow:



(racemic α-bromopropiophenone) (Compound 1)

Muller et al do not disclose the use of an optically active amine in the production of their compounds 1, and one of ordinary skill in the art would understand that Muller et al disclose the use of a racemic amine. Since Muller et al disclose the use of racemic α-bromopropiophenone and a racemic amine, the ketone compounds 1 disclosed in Muller et al would not be optically active, which is confirmed by the entire disclosure of Muller et al which refers to the reduction of a "racemic" α-phenylalkylamino propiophenone.

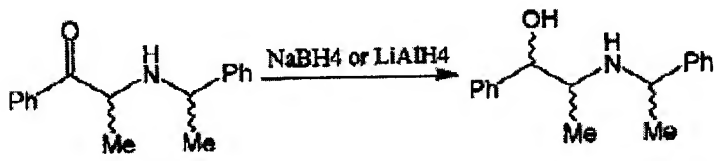
In Muller et al, the ketone compound 1 is a mixture of four isomers, which include diasteromers and two pairs of enantiomers. Applicants illustrate this with respect to the ketone compound 1b.



The mixture of four aminoketone isomers in Muller et al is not optically active. Muller et al nowhere disclose or suggest isolating an optically active compound from their mixture of four aminoketone isomers. Muller et al disclose reducing the mixture to form an aminoalcohol, as set forth in the next section of Muller et al.

(2) Synthesis of 2-Phenylalkylamino-l-phenylpropanol

Thus, Muller et al disclose, at page 451, line 23+ that 2-phenylalkylamino-l-phenylpropanol is obtained by reducing the AP-Derivative (compound 1) in the presence of a reducing agent such as $NaBH_4$ or $LiAlH_4$. Applicants illustrate this reaction as follows:



Accordingly, Muller et al do not disclose a process for producing an optically active α-substituted aminoketone of formula (4) or an optically active α-substituted aminoketone salt of formula (5), and do not disclose or suggest the use of an optically active amine represented by formula (2) of the present claims.

In general, Muller et al do not disclose a process for producing an optically active α-substituted aminoketone of formula (3), and do not disclose the step of isolating an optically active compound from a mixture of diastereomers.

Thus, Muller et al differ from the present invention as set forth in claim 1 because Muller et al do not disclose or suggest a process for producing an optically active α-substituted aminoketone represented by formula (4) or the optically active α-substituted aminoketone salt of

formula (5), do not disclose or suggest employing an optically active amine represented by formula (2) to produce a mixture of diastereomers of an optically active α-substituted aminoketone of formula (3), and do not disclose or suggest isolating one diastereomer from a mixture of diastereomers of an optically active α-substituted aminoketone represented by formula (3) after optionally yielding salts of the diastereomers with an acid.

Further, with respect to claim 9, Muller et al do not disclose or suggest the use of methanesulfonic acid.

Similarly, with respect to claim 71, Muller et al do not disclose or suggest a process for producing an optically active α-substituted aminoketone represented by formula (4) or an optically active α-substituted aminoketone salt of formula (5), and do not disclose or suggest isolating one diastereomer from a mixture of diastereomers of an optically active α-substituted aminoketone represented by formula (3) after optionally yielding salts of the diastereomers with an acid.

The Examiner acknowledges that applicants have argued that Muller et al disclose racemic amine instead of an optically active amine. The Examiner responds by stating that inasmuch as the [Muller et al] process involves production of enantiomers using methanesulfonic acids, the use of a racemic and optically active amine would produce the same results, absent evidence to the contrary. The Examiner cites *In re Adamson*, 125 USPQ 233, in support of his position.

The Examiner further states that applicants have submitted arguments with respect to compound 1b on pages 450 and 452. The Examiner states that he again relies on the above case law.

In response, applicants first point out that the Muller et al process does not involve production of enantiomers using methanesulfonic acid. Muller et al nowhere disclose or suggest the use of methanesulfonic acid. The use of methanesulfonic acid in Muller et al is an undefined hypothetical process imagined by the Examiner based on the disclosure of Matsuo et al, but as discussed in detail below, Matsuo et al do not disclose or suggest the use of methansulfonic acid as an optically active agent.

Further, with respect to the Examiner's reliance on *In re Adamson*, applicants point out that the claim on appeal in *Adamson* was directed to an l-isomer of a racemic mixture containing two sterioisomers having a single asymmetric carbon atom. It was not directed to a process for producing an isomer. *Adamson* was based on the proposition that a racemic mixture composed of two stereoisomers generally is known in the art as being a mixture in which the two stereoisomers are separable from each other.

In contrast, the present invention is directed to a process of producing a diastereomer having two asymmetric carbon atoms. The *Adamson* case was not concerned with diastereomers having two asymmetric carbon atoms and therefore is not relevant to the present invention.

Further, the Examiner's statement that the use of racemic and optically active amines would produce the same results is not correct.

The use of a racemic amine in Muller et al does not produce compounds that would be optically active. As discussed above, in Muller et al, the final product is a mixture of four isomers which includes diasteriomers and two pairs of enantiomers. This mixture of Muller et al is not optically active and is not separated into optically active aminoketones by Muller et al.

There simply is no disclosure or suggestion in the cited prior art to employ an optically active amine represented by formula (2) to produce a mixture of diastereomers of an optically active α-substituted aminoketone of formula (3). In the absence of a teaching or suggestion of such a step in Muller et al or elsewhere, Muller et al do not render obvious the recitations of claim 1. The Examiner has failed to recognize that this a required step of claim 1, and has failed to provide any reason why one of ordinary skill in the art would modify the teachings of Muller et al to provide this step.

Turning now to Matsuo et al, the Examiner states that

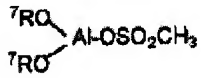
> Matsuo et al is teaching a process of preparing optically active amino ketone, wherein it is expressly taught that use of methanesulfonic acid is old in the preparation of optically active amino ketone, see for example, column 8 and various examples.

But the examiner's understanding is not correct.

Matsuo at al nowhere disclose or suggest a process of preparing an optically active aminoketone by use of methanesulfonic acid, and nowhere disclose or suggest a process of separating aminoketone diastereomers by methanesulfonic acid. Instead, Matsuo et al disclose a process for preparing an aminoalcohol starting from an already produced aminoketone.

Thus, Matsuo et al relate to preparing an **aminoalcohol** from an aminoketone, and methanesulfonic acid is used to prepare the amino alcohol, and is not used to prepare an

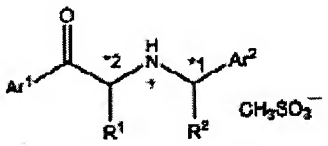
aminoketone. In Matsuo et al, methanesulfonic acid reacts with **an** aluminum compound and the following reducing agent is formed.



This reducing agent in Matsuo et al is then reacted with an aminoketone compound of general formula (1) of Matsuo et al to form an aminoalcohol of general formula (7) of Matsuo et al.

Thus, Matsuo et al disclose the use of methanesulfonic acid as a reactive ingredient which reacts with an organoaluminum compound of general formula (4) of Matsuo et al and an alcohol compound of general formula (6) of Matsuo et al to form a reducing agent. This reducing agent is then reacted with an aminoketone compound of general formula (1) of Matsuo et al to form an aminoalcohol of general formula (7) of Matsuo et al.

On the other hand, in the present invention, when methanesulfonic acid is employed, it reacts with an aminoketone compound represented by the general formula (3) and the following salt is formed.



Thus, in the present invention, the acid is optionally employed to isolate one diastereomer from a mixture of diastereomers of an optically active aminoketone by preparing a salt of the compound of formula (3) with an acid.

Matsuo et al do not disclose the use of an acid to prepare a salt of a compound of formula (3) to isolate a diastereomer, but rather disclose the use of an acid to form a reducing agent, which is then reacted with an already prepare aminoketone starting compound. In Matsuo et al, there is no isolation of an optically active aminoketone compound from a mixture of diastereomers. Accordingly, Matsuo et al do not supply the deficiencies of Muller et al.

Furthermore, in the examples of Matsuo et al, a carbamate type protecting group is used as a protecting group of an amino group of an aminoketone. But it is clear to one of ordinary skill in the art that an amine protected by a carbamate type protecting group does not form a salt with an acid. Thus, the addition of methansulfonic acid to aminoketones having a carbamate protected amino group in Matsuo et al does not form a salt. This fact also shows that the present invention is completely different from Matsuo et al.

Accordingly, even if Muller et al and Matsuo et al are combined, they do not lead to the present invention.

The Examiner also states that although Muller et al may not teach methanesulfonic acid, Matsuo et al expressly teach the use of methanesulfonic acid. The Examiner states that applicants' arguments concerning methanesulfonic acid having a different purpose in Matsuo et al is of little probative value, because methanesulfonic acid is very well known for obtaining an optically active agent.

With respect to the Examiner's argument that methanesulfonic acid is a very well known agent for obtaining an optically active agent, applicants submit that the Examiner is not correct.

Applicants have never heard that methanesulfonic acid is generally used for obtaining an optically active agent.

Applicants cannot remember a good example. Methanesulfonic acid is a non-optically active compound and one of ordinary skill in the art never uses it for an optical separation. Further, as discussed above, Matsuo et al nowhere disclose or suggest a process of preparing an optically active aminoketone by use of methanesulfonic acid

Further, claims 13 and 14 recite the use of a hydrogen halide as the acid to be used in the isolation. Muller et al and Matsuo et al do not disclose use of such an acid.

In general, the steps that are disclosed in Muller et al and Matsuo et al are not those of the present invention. The Examiner has not provided any rational reason why it would be obvious to modify the steps of Muller et al to arrive at the steps of the present invention. The modifications that the Examiner proposes, to the extent they can be understood, do not result in the steps of the present invention. Thus, for example, the Examiner nowhere proposes that it would be obvious to employ an optically active amine in Muller et al. Without such a step, claim 1 is not rendered obvious. In Muller et al, there is no description of producing **an** optically active compound and all compounds are non-optically active compounds.

In Muller at al, there is no disclosure of separating aminoketone diastereomers, as above-mentioned. Similarly, there is no disclosure in Matsuo et al that would lead one of ordinary skill in the art to separating the aminoketone mixture of Muller et al and isolating one diastereomer from a mixture of two diastereomers of an optically active α-substituted aminoketone represented by formula (3).

In view of the above, applicants submit that Muller et al and Matsuo et al do not disclose or render obvious the subject matter of the above claims and, accordingly, request withdrawal of this rejection.

Claims 47-54 have been rejected under 35 U.S.C. § 103(a) as obvious over Muller et al, optionally in view of Matsuo et al.

Applicants submit that Muller et al and Matsuo et al do not disclose or render obvious the subject matter of the above claims and, accordingly, request withdrawal of this rejection.

Claims 47-54 are directed to an optically active α-substituted aminoketone of formula (4) or an optically active α-substituted aminoketone salt represented by formula (5).

The Examiner states that Muller et al disclose, at page 451, lines 11-21, compounds that are structurally similar to those of the present claims. The Examiner states that the difference between Muller et al and the presently claimed compounds is that Muller et al do not disclose optical isomerism of the compounds.

The Examiner argues that it would have been obvious to obtain stereoisomers of the Muller et al compounds. The Examiner states that Matsuo et al specifically teach a process for obtaining optically active compounds. The Examiner states that Muller et al also use stereoselection, as disclosed at page 451, line 6.

As discussed above, Matsuo et al disclose the use of methanesulfonic acid as a reactive ingredient which reacts with an organoaluminum compound of general formula (4) of Matsuo et al and an alcohol compound of general formula (6) of Matsuo et al to form a reducing agent. This reducing agent is then reacted with an aminoketone starting compound of general formula (1) of Matsuo et al to form an aminoalcohol of general formula (7) of Matsuo et al. Matsuo et al do not disclose or suggest that the method they disclose can be used to form an optically active α-substituted aminoketone of formula (4) or an optically active α-substituted aminoketone salt of formula (5).

As set forth in the present specification, an optically active compound represented by formula (4) or (5) with R^1 representing a C_1-C_4 alkyl group or a C_7-C_{12} aralkyl group is a new molecular entity not disclosed or suggested in any literature heretofore.

The Examiner responds to the arguments that applicants submitted by stating that methanesulfonic acid is a well known agent for obtaining stereoisomers.

As discussed above, with respect to the Examiner's argument that methanesulfonic acid is a very well known agent for obtaining an optically active agent, applicants submit that the Examiner is not correct.

Applicants have never heard that methanesulfonic acid is generally used for obtaining an optically active agent.

Applicants cannot remember a good example. Methanesulfonic acid is a non-optically active compound and one of ordinary skill in the art never uses it for an optical separation.

Further, as discussed above, Matsuo et al nowhere disclose or suggest a process of preparing an optically active aminoketone by use of methanesulfonic acid

The Examiner also refers to *Sterling Drug v. Watson*, the correct cite for which is 108 USPQ 37. Applicants submit that this case is not applicable to the present facts. In *Sterling Drug*, the compound being claimed was an isomer of a racemic mixture containing two isomers having a single asymmetric carbon atom, and not a stereoisomer having two asymmetric carbon atoms as in the present claims. Since the *Sterling Drug* case was not concerned with a claimed stereoisomer having two asymmetric carbon atoms, applicants submit that *Sterling Drug* is not relevant to the present claims.

With respect to the Examiner reference to page 451, line 6 of Muller et al where Muller et al describe a stereoselectivity, the stereoselectivity means relative steric configuration of diasteriomers, that is, erythro and threo. According to Muller et al, one can obtain compounds which are rich in one stereoisomer. But the stereoselectivity is that of an alcohol obtained by reduction of a ketone. This reaction is explained in detail at the experimental section of page 458, in which a salt of an α-aminoketone with hydrochloride is reduced by $NaBH_4$ in methanol, water, or dimethylformamide. Also, scheme (2) of page 454 shows the reason for the stereoselectivity, that is, an erythro compound is produced by the reductive reaction by $NaBH_4$. But the erythro compound is not an optically active compound, but a racemic compound. Thus, the stereoselectivity at page 451 of Muller et al has nothing to do with a stereoselection of an optically active α-substituted aminoketone of formula (4) or an optically active α-substituted aminoketone salt of formula (5). The obtained compounds in Muller et al include two enantiomers and it is impossible to separate the enantiomers by the procedure of Muller et al.

In view of the above, applicants submit that Muller et al and Matsuo et al do not disclose or render obvious the subject matter of the above claims and, accordingly, request withdrawal of this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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